Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength.

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Public Summary:
Sarcopenia is an aging-associated muscle wasting disease that lacks good treatment options. In this manuscript the authors show that blocking the activity of a single protein called 15-PGDH in old mice for one month restores mass and strength to the animals' withered muscles and helps them run longer on a treadmill, rejuvenating their muscles. Conversely, increasing the abundance of the protein in young mice causes their muscles to atrophy and weaken, effectively prematurely aging the muscles of these mice. 15-PGDH breaks down another molecule called PGE2. Blocking its activity effectively increases the amount of PGE2 present in aged muscles. PGE2 signaling in turn impacts cellular pathways to ameliorate muscle atrophy and rejuvenate muscle function. 15-PGDH may be a suitable therapeutic target for countering sarcopenia.

Scientific Abstract:
Treatments are lacking for sarcopenia, a debilitating age-related skeletal muscle wasting syndrome. We identifed increased amounts of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the prostaglandin E2 (PGE2)-degrading enzyme, as a hallmark of aged tissues, including skeletal muscle. The consequent reduction in PGE2 signaling contributed to muscle atrophy in aged mice and results from 15-PGDH-expressing myofibers and interstitial cells, such as macrophages, within muscle. Overexpression of 15-PGDH in young muscles induced atrophy. Inhibition of 15-PGDH, by targeted genetic depletion or a small-molecule inhibitor, increased aged muscle mass, strength, and exercise performance. These benefits arise from a physiological increase in PGE2 concentrations, which augmented mitochondrial function and autophagy and decreased transforming growth factor-beta signaling and activity of ubiquitin-proteasome pathways. Thus, PGE2 signaling ameliorates muscle atrophy and rejuvenates muscle function, and 15-PGDH may be a suitable therapeutic target for countering sarcopenia.